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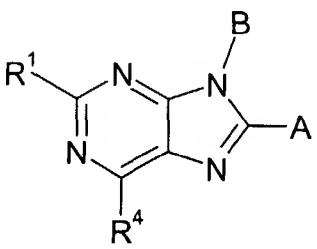
(54) Title: PURINE COMPOUNDS AND USES THEREOF AS CANNABINOID RECEPTOR LIGANDS



(I)

(57) Abstract: Compounds of Formula (I) that act as cannabinoid receptor ligands and their uses in the treatment of diseases linked to the mediation of the cannabinoid receptors in animals are described herein.

PURINE COMPOUNDS AND USE THEREOF AS CANNABINOID RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention relates to purine compounds and intermediates useful in the synthesis of the purine compounds. The purine compounds are useful as cannabinoid receptor ligands, in particular as CB-1 receptor antagonists. As a result, the present invention also relates to the use of the purine compounds in treating diseases, conditions and disorders modulated by cannabinoid receptor ligands including pharmaceutical compositions for such use.

BACKGROUND

Obesity is a major public health concern because of its increasing prevalence and associated health risks. Obesity and overweight are generally defined by body mass index (BMI), which is correlated with total body fat and estimates the relative risk of disease. BMI is calculated by weight in kilograms divided by height in meters squared (kg/m^2). Overweight is typically defined as a BMI of 25-29.9 kg/m^2, and obesity is typically defined as a BMI of 30 kg/m^2. See, e.g., National Heart, Lung, and Blood Institute, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, Washington, DC: U.S. Department of Health and Human Services, NIH publication no. 98-4083 (1998).

The increase in obesity is of concern because of the excessive health risks associated with obesity, including coronary heart disease, strokes, hypertension, type 2 diabetes mellitus, dyslipidemia, sleep apnea, osteoarthritis, gall bladder disease, depression, and certain forms of cancer (e.g., endometrial, breast, prostate, and colon). The negative health consequences of obesity make it the second leading cause of preventable death in the United States and impart a significant economic and psychosocial effect on society. See, McGinnis M, Foege WH., "Actual Causes of Death in the United States," JAMA, **270**, 2207-12 (1993).

Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. Although weight loss is an important treatment outcome, one of the main goals of obesity management is to improve cardiovascular and metabolic values to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as blood glucose, blood pressure, and lipid concentrations. Hence, it is believed that a 5-10% intentional reduction in body weight may reduce morbidity and mortality.

Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. Satiety is achieved by increasing synaptic levels of norepinephrine, serotonin, or both. For example, stimulation of serotonin receptor subtypes 1B, 1D, and 2C and 1- and 2-adrenergic receptors decreases food intake by regulating satiety. See, Bray GA, "The New Era of Drug Treatment. Pharmacologic Treatment of Obesity: Symposium Overview," Obes Res., **3**(suppl 4), 415s-7s (1995). Adrenergic agents (e.g., diethylpropion, benzphetamine, phendimetrazine, mazindol, and phentermine) act by modulating central norepinephrine and dopamine receptors through the promotion of catecholamine release. Older adrenergic weight-loss drugs (e.g., amphetamine, methamphetamine, and phenmetrazine), which strongly engage in dopamine pathways, are no longer recommended because of the risk of their abuse. Fenfluramine and dexfenfluramine, both serotonergic agents used to regulate appetite, are no longer available for use.

More recently, CB1 cannabinoid receptor antagonists/inverse agonists have been suggested as potential appetite suppressants. See, e.g., Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997); Colombo, G., *et al.*, "Appetite Suppression and Weight Loss after the Cannabinoid Antagonist SR141716," Life Sci., **63**, PL113-PL117 (1998); Simiand, J., *et al.*, "SR141716, a CB1 Cannabinoid Receptor Antagonist, Selectively Reduces Sweet Food Intake

in Marmose," Behav. Pharmacol., **9**, 179-181 (1998); and Chaperon, F., *et al.*, "Involvement of Central Cannabinoid (CB1) Receptors in the Establishment of Place Conditioning in Rats," Psychopharmacology, **135**, 324-332 (1998). For a review of cannabinoid CB1 and CB2 receptor modulators, see Pertwee, R.G., "Cannabinoid Receptor Ligands: Clinical and Neuropharmacological Considerations, Relevant to Future Drug Discovery and Development," Exp. Opin. Invest. Drugs, **9**(7), 1553-1571 (2000).

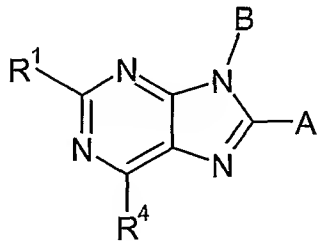
Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment for reducing or preventing weight-gain.

In addition to obesity, there also exists an unmet need for treatment of alcohol abuse. Alcoholism affects approximately 10.9 million men and 4.4 million women in the United States. Approximately 100,000 deaths per year have been attributed to alcohol abuse or dependence. Health risks associated with alcoholism include impaired motor control and decision making, cancer, liver disease, birth defects, heart disease, drug/drug interactions, pancreatitis and interpersonal problems. Studies have suggested that endogenous cannabinoid tone plays a critical role in the control of ethanol intake. The endogenous CB1 receptor antagonist SR-141716A has been shown to block voluntary ethanol intake in rats and mice. See, Arnone, M., *et al.*, "Selective Inhibition of Sucrose and Ethanol Intake by SR141716, an Antagonist of Central Cannabinoid (CB1) Receptors," Psychopharmacol, **132**, 104-106 (1997). For a review, see Hungund, B.L and B.S. Basavarajappa, "Are Anadamide and Cannabinoid Receptors involved in Ethanol Tolerance? A Review of the Evidence," Alcohol & Alcoholism. **35**(2) 126-133, 2000.

Current treatments for alcohol abuse or dependence generally suffer from non-compliance or potential hepatotoxicity; therefore, there is a high unmet need for more effective treatment of alcohol abuse/dependence.

SUMMARY

The present invention provides compounds of Formula (I) that act as cannabinoid receptor ligands (in particular, CB1 receptor antagonists)



(I)

wherein

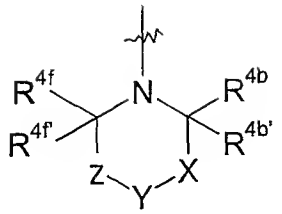
A is an optionally substituted aryl or an optionally substituted heteroaryl (preferably, A is a substituted phenyl, more preferably a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl (preferably fluoro-substituted alkyl), and cyano, most preferably, A is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl);

B is an optionally substituted aryl or an optionally substituted heteroaryl (preferably, B is a substituted phenyl, more preferably a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl (preferably fluoro-substituted alkyl), and cyano, most preferably, B is 4-chlorophenyl or 4-fluorophenyl);

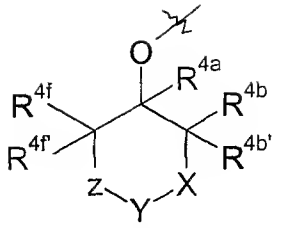
R^1 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy (preferably, R^1 is hydrogen, methyl, ethyl, halo-substituted methyl or ethyl, or (C_1-C_4)alkoxy; more preferably, R^1 is hydrogen, methyl, ethyl, fluoro-substituted methyl or ethyl, or (C_1-C_4)alkoxy; most preferably, R^1 is hydrogen, methyl, or fluoro-substituted methyl);

R^4 is

(i) a group having Formula (IA) or Formula (IB)



(IA)



(IB)

where R^{4a} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl)$_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, $((C_1\text{-}C_4)$alkyl)$_2$amino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2$- or $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $((C_1\text{-}C_4)$alkyl)$_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, di$(C_1\text{-}C_4)$alkylamino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, -C(=N-OH)-, or -C(R^{4d})($R^{4d'}$)-, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, ((C_1-C_4)alkyl)$_2$N-C(O)-, HO-NH-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated, 3- to 6-membered heterocyclic ring, a 5- or 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is –N$R^{4d''}$-, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted;

Z is a bond, –CH_2CH_2-, or -C(R^{4e})($R^{4e'}$)-, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, ((C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

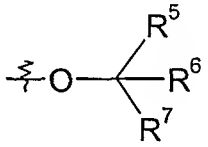
or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, acyloxy, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $((C_1$-$C_4)$alkyl$)_2$N-C(O)-, $(C_1$-$C_6)$alkylamino-, di$(C_1$-$C_4)$alkylamino-, $(C_3$-$C_6)$cycloalkylamino-, acylamino-, aryl$(C_1$-$C_4)$alkylamino-, heteroaryl$(C_1$-$C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge;

provided that when R^4 is a group of Formula (IA), then (a) at least one of R^{4b}, $R^{4b'}$, R^{4c}, $R^{4c'}$, R^{4d}, $R^{4d'}$, $R^{4d''}$, R^{4e}, $R^{4e'}$, R^{4f} and $R^{4f'}$ is other than hydrogen, $(C_1$-$C_4)$alkyl, or halo-substituted $(C_1$-$C_4)$alkyl; and (b) Y is not oxygen, sulfur or -NH-, when X and Z are a bond, $-CH_2$- or $-CH_2CH_2$-, and R^{4b}, $R^{4b'}$, R^{4f} and $R^{4f'}$ are hydrogen; or

(ii) a group having Formula (IC)



(IC)

where R^5 and R^6 are each independently hydrogen or $(C_1$-$C_4)$alkyl, and R^7 is $(C_1$-$C_4)$alkyl-, halo-substituted $(C_1$-$C_4)$alkyl-, $(C_1$-$C_4)$alkoxy$(C_1$-$C_4)$alkyl-, $(C_1$-$C_4)$alkylamino$(C_1$-$C_4)$alkyl-, di$(C_1$-$C_4)$alkylamino$(C_1$-$C_4)$alkyl-, or a partially or fully saturated 4- to 6-membered heterocylic ring containing 1 to 2 heteroatoms independently selected from oxygen, sulfur or nitrogen,

or R^5 and R^6 or R^5 and R^7 taken together form a 5- or 6-membered lactone, 4- to 6-membered lactam, or a 4- to 6-membered partially or fully saturated heterocycle containing 1 to 2 heteroatoms independently selected

from oxygen, sulfur or nitrogen, where the lactone, the lactam and the heterocycle are optionally substituted;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

A preferred compound of the present invention is a compound of Formula (I) where R^4 is a group of Formula (IA). Preferably, R^{4b} and $R^{4b'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2$- or $-C(R^{4c})(R^{4c'})$-, where R^{4c} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, acyloxy, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, $(C_1$-$C_6)$alkylamino-, $((C_1$-$C_4)$alkyl$)_2$amino-, $(C_3$-$C_6)$cycloalkylamino-, acylamino-, aryl$(C_1$-$C_4)$alkylamino-, heteroaryl$(C_1$-$C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4c} taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge, and $R^{4c'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or -C(R^{4d})($R^{4d'}$)-, where R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, ((C_1-C_4)alkyl)$_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, and $R^{4d'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl)$_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated, 3- to 6-membered heterocyclic ring, a 5- or 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is –N$R^{4d''}$-, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted;

Z is a bond, –CH_2CH_2-, or -C(R^{4e})($R^{4e'}$)-, where R^{4e} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, ((C_1-C_4)alkyl)$_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully

saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4e} taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge, and $R^{4e'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Preferably, R^{4b} is hydrogen, an optionally substituted $(C_1$-$C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge; $R^{4b'}$ is hydrogen, an optionally substituted $(C_1$-$C_3)$alkyl, or taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge; R^{4f} is hydrogen, an optionally substituted $(C_1$-$C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge; and $R^{4f'}$ is hydrogen, an optionally substituted $(C_1$-$C_3)$alkyl, or taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge, and even more preferably, R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen.

When Y is $-NR^{4d''}$-, then $R^{4d''}$ is preferably a hydrogen or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl,

(C_1-C_3)alkylsulfonyl, (C_1-C_3)alkylaminosulfonyl, di(C_1-C_3)alkylaminosulfonyl, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted (more preferably, $R^{d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_3)alkylsulfonyl, (C_1-C_3)alkylaminosulfonyl, di(C_1-C_3)alkylaminosulfonyl, acyl, (C_1-C_6)alkyl-O-C(O)-, and heteroaryl, where the moiety is optionally substituted (preferably the (C_1-C_3)alkylsulfonyl, (C_1-C_3)alkylaminosulfonyl, di(C_1-C_3)alkylaminosulfonyl, acyl, and (C_1-C_6)alkyl-O-C(O)- are optionally substituted with 1 to 3 fluorines, and the heteroaryl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, (C_1-C_3)alkoxy, (C_1-C_3)alkyl, and fluoro-substituted (C_1-C_3)alkyl);

X is -C(R^{4c})($R^{4c'}$)-, where R^{4c} and $R^{4c'}$ are each independently hydrogen, $H_2NC(O)$-, an optionally substituted (C_1-C_6)alkyl, (C_1-C_4)alkyl-NH-C(O)-, or ((C_1-C_4)alkyl)$_2$N-C(O)-, or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge; and

Z is -C(R^{4e})($R^{4e'}$)-, where R^{4e} and $R^{4e'}$ are each independently hydrogen, $H_2NC(O)$-, an optionally substituted (C_1-C_6)alkyl, (C_1-C_4)alkyl-NH-C(O)-, or ((C_1-C_4)alkyl)$_2$N-C(O)-, or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge.

When Y is -C(R^{4d})($R^{4d'}$)-, then R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, ((C_1-C_4)alkyl)$_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted (preferably, R^{4d} is amino, (C_1-C_6)alkylamino, di(C_1-C_4)alkylamino, (C_3-C_6)cycloalkylamino, acylamino, aryl(C_1-C_4)alkylamino-, or heteroaryl(C_1-C_4)alkylamino, more

preferably, R^{4d} is amino, (C_1-C_6)alkylamino, di(C_1-C_4)alkylamino, (C_3-C_6)cycloalkylamino), and

$R^{4d'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted (preferably, $R^{4d'}$ is (C_1-C_6)alkyl, $H_2NC(O)$-, (C_1-C_4)alkyl-NH-C(O)-, or $((C_1-C_4)$alkyl$)_2$N-C(O)-, or aryl, more preferably, $R^{4d'}$ is $H_2NC(O)$-, (C_1-C_4)alkyl-NH-C(O)-, or $((C_1-C_4)$alkyl$)_2$N-C(O)-),

or R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated, 3- to 6-membered heterocyclic ring, a 5- to 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

X is a bond or $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each hydrogen; and Z is a bond or $-C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each hydrogen.

Another preferred embodiment is a compound where Y is $-C(R^{4d})(R^{4d'})$-, R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen; R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_6)alkylamino-, and di(C_1-C_4)alkylamino-, where the moiety is optionally substituted (preferably, R^{4d} is hydrogen, hydroxy, amino, or a chemical moiety selected from the group consisting of (C_1-C_6)alkoxy, acyl, (C_1-C_6)alkylamino-, and di(C_1-C_4)alkylamino-); and $R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, aryl and heteroaryl, where the moiety is optionally substituted (preferably, $R^{4d'}$ is hydrogen, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl and aryl, where the moiety is optionally substituted). In this embodiment, X is preferably $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each

independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge (preferably, R^{4c} and $R^{4c'}$ are each hydrogen or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond); and Z is preferably -$C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge (preferably, R^{4e} and $R^{4e'}$ are each hydrogen or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond).

Yet another preferred embodiment is a compound where Y is -$C(R^{4d})(R^{4d'})$-, R^{4b}, $R^{4b'}$, R^{4f}, and $R^{4f'}$ are all hydrogen; and R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated 3- to 6-membered heterocyclic ring, a 5- to 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring or the lactam ring optionally contains an additional heteroatom selected from oxygen, nitrogen or sulfur (preferably, R^{4d} and $R^{4d'}$ taken together form a 5 to 6 membered lactam ring, where the lactam ring is optionally substituted and optionally contains an additional heteroatom selected from nitrogen or oxygen). In this embodiment, X is preferably a bond, $-CH_2CH_2$- or -$C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4c} or $R^{4c'}$ taken together with R^{4e} or $R^{4e'}$ forms a bond, a methylene bridge or an ethylene bridge (more preferably, X is a bond or -$C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each hydrogen); and Z is preferably a bond, $-CH_2CH_2$- or -$C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each independently hydrogen or an optionally substituted (C_1-C_6)alkyl, or either R^{4e} or $R^{4e'}$ taken together with R^{4c} or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge (more preferably, Z is a bond or -$C(R^{4e})(R^{4e'})$-, where R^{4e} and $R^{4e'}$ are each hydrogen).

Another preferred compound of the present invention is a compound of Formula (I) where R^4 is a group of Formula (IB) where where R^{4a} is as

defined above, R^{4b} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, acyloxy, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, $(C_1$-$C_6)$alkylamino-, $((C_1$-$C_4)$alkyl$)_2$amino-, $(C_3$-$C_6)$cycloalkylamino-, acylamino-, aryl$(C_1$-$C_4)$alkylamino-, heteroaryl$(C_1$-$C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

$R^{4b'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2$- or $-C(R^{4c})(R^{4c'})$-, where R^{4c} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, acyloxy, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, $(C_1$-$C_6)$alkylamino-, $((C_1$-$C_4)$alkyl$)_2$amino-, $(C_3$-$C_6)$cycloalkylamino-, acylamino-, aryl$(C_1$-$C_4)$alkylamino-, heteroaryl$(C_1$-$C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4c} taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge, and $R^{4c'}$ is hydrogen, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1$-$C_6)$alkyl, acyl, $(C_1$-$C_3)$alkyl-O-C(O)-, $(C_1$-$C_4)$alkyl-NH-C(O)-, $(C_1$-$C_4)$alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge (preferably, X is

a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen or (C_1-C_6)alkyl);

Y is oxygen, sulfur, -C(O)-, or $-C(R^{4d})(R^{4d'})-$, where R^{4d} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)$alkyl$)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, and $R^{4d'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated, 3- to 6-membered heterocyclic ring, a 5- or 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted (preferably, Y is $-NR^{4d''}-$, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted);

Z is a bond, $-CH_2CH_2-$, or $-C(R^{4e})(R^{4e'})-$, where R^{4e} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)$alkyl$)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or R^{4e} taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge, and $R^{4e'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted, or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge (preferably, Z is a bond, $-CH_2CH_2-$ or $-C(R^{4c})(R^{4c'})-$, where R^{4c} and $R^{4c'}$ are each independently hydrogen or (C_1-C_6)alkyl);

R^{4f} is hydrogen, cyano, hydroxy, amino, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, (C_1-C_6)alkylamino-, $((C_1-C_4)$alkyl$)_2$amino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted; and

$R^{4f'}$ is hydrogen, $H_2NC(O)-$, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, (C_1-C_4)alkyl$)_2$N-C(O)-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge, or an ethylene bridge;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

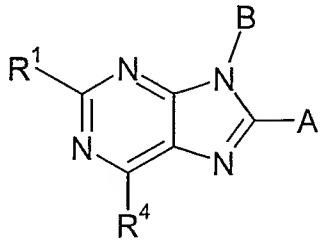
Yet another preferred compound of the present invention is a compound of Formula (I) where R^4 is a group of Formula (IC), where where R^5 and R^6 are each independently hydrogen or (C_1-C_4)alkyl, and R^7 is (C_1-C_4)alkyl-, halo-substituted (C_1-C_4)alkyl-, (C_1-C_4)alkoxy(C_1-C_4)alkyl-, (C_1-C_4)alkylamino(C_1-C_4)alkyl-, di(C_1-C_4)alkylamino(C_1-C_4)alkyl-, or a partially or fully saturated 4- to 6-membered heterocylic ring containing 1 to 2 heteroatoms independently selected from oxygen, sulfur or nitrogen, or R^5 and R^6 or R^5 and R^7 taken together form a 5- to 6-membered lactone, 4- to 6-membered lactam, or a partially or fully saturated 4- to 6-membered heterocycle containing 1 to 2 heteroatoms independently selected from oxygen, sulfur or nitrogen, where the lactone, the lactam and the heterocycle are optionally substituted; a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug. Preferably, R^5 and R^6 are each independently hydrogen or (C_1-C_4)alkyl, and R^7 is (C_1-C_4)alkyl.

Preferred compounds of the present invention include: 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 1-{1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-yl}-ethanone; {3-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-3-(1α,5α,6α)-azabicyclo[3.1.0]hex-6-yl}-dimethylamine; 6-(1-benzylpyrrolidin-3-yloxy)-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-6-(1-cyclohexylazetidin-3-yloxy)-8-(2,4-dichlorophenyl)-9H-purine; 6-tert-butoxy-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-isopropoxy-9H-purine; 1-[9-(4-chlorophenyl)-8-(2,4-

dichlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-2-methyl-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-pyrrolidin-1-yl-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 4-amino-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-4-methylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chloro-phenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 8-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 9-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-methyl-4-oxa-1,9-diazaspiro[5.5]undecan-2-one; 8-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-ol; 4-benzyl-1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidin-4-ol; 4-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperazine-2-carboxylic acid methylamide; 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-9H-purine; and 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-(4-pyrimidin-2-yl-piperazin-1-yl)-9H-purine; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound or the salt.

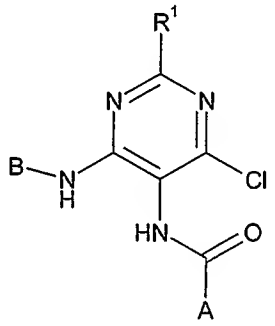
Preferred pharmaceutically acceptable salts include hydrochloride, mesylate and besylate salts. In some instances, the free base is preferred. "Free base" refers to an amino group having a lone pair of electrons.

Another embodiment of the present invention includes intermediates (1c/d) and (1b) which are useful in the synthesis of the compounds of the present invention:



(1c/d)

wherein A and B are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, and cyano; R^1 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; and R^4 is hydroxy or halo; and



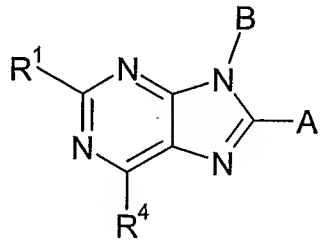
(1b)

wherein A and B are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, and cyano; and R^1 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy.

Preferably, A and B are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl), and cyano. More preferably, A is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and B is 4-chlorophenyl or 4-fluorophenyl.

Yet another embodiment of the present invention includes a pharmaceutical composition comprising (1) a compound of the present invention and (2) a pharmaceutically acceptable excipient, diluent, or carrier. Preferably, the composition comprises a therapeutically effective amount of a compound of the present invention. The composition may also contain at least one additional pharmaceutical agent (described herein). Preferred agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone and nalmefene), dopaminergic agents (e.g., apomorphine), attention deficit activity disorder (ADHD) agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and anti-obesity agents (described herein below).

Yet another embodiment of the present invention includes a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (in particular, a CB1 receptor) antagonist in animals comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Formula (II) (or a pharmaceutical composition thereof).



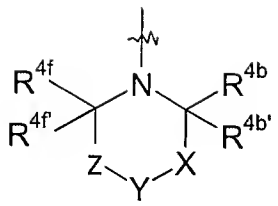
(II)

wherein

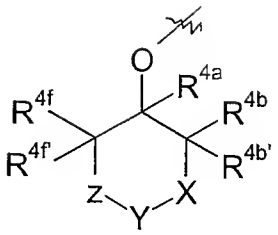
A is an optionally substituted aryl or an optionally substituted heteroaryl; B is an optionally substituted aryl or an optionally substituted heteroaryl; R^1 is hydrogen, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or (C_1-C_4)alkoxy;

R^4 is

(i) a group having Formula (IA) or Formula (IB)



(IA)



(IB)

where R^{4a} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{4b} and $R^{4b'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $(C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, $((C_1\text{-}C_4)$alkyl$)_2$amino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4b} or $R^{4b'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge, or an ethylene bridge;

X is a bond, $-CH_2CH_2$- or $-C(R^{4c})(R^{4c'})$-, where R^{4c} and $R^{4c'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyloxy, acyl, $(C_1\text{-}C_3)$alkyl-O-C(O)-, $(C_1\text{-}C_4)$alkyl-NH-C(O)-, $((C_1\text{-}C_4)$alkyl$)_2$N-C(O)-, $(C_1\text{-}C_6)$alkylamino-, di$(C_1\text{-}C_4)$alkylamino-, $(C_3\text{-}C_6)$cycloalkylamino-, acylamino-, aryl$(C_1\text{-}C_4)$alkylamino-, heteroaryl$(C_1\text{-}C_4)$alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4c} or $R^{4c'}$ taken together with R^{4e}, $R^{4e'}$, R^{4f}, or $R^{4f'}$ forms a bond, a methylene bridge or an ethylene bridge;

Y is oxygen, sulfur, -C(O)-, or -C(R^{4d})($R^{4d'}$)-, where R^{4d} and $R^{4d'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, ((C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or R^{4d} and $R^{4d'}$ taken together form a partially or fully saturated, 3- to 6-membered heterocyclic ring, a 5- or 6-membered lactone ring, or a 4- to 6-membered lactam ring, where the heterocyclic ring, the lactone ring and the lactam ring are optionally substituted and the lactone ring and the lactam ring optionally contain an additional heteroatom selected from oxygen, nitrogen or sulfur, or

Y is –$NR^{4d''}$-, where $R^{4d''}$ is a hydrogen or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_3)alkylsulfonyl-, (C_1-C_3)alkylaminosulfonyl-, di(C_1-C_3)alkylaminosulfonyl-, acyl, (C_1-C_6)alkyl-O-C(O)-, aryl, and heteroaryl, where the moiety is optionally substituted;

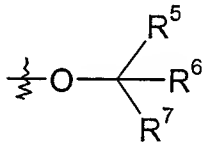
Z is a bond, –CH_2CH_2-, or -C(R^{4e})($R^{4e'}$)-, where R^{4e} and $R^{4e'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, ((C_1-C_4)alkyl)$_2$N-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4e} or $R^{4e'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; and

R^{4f} and $R^{4f'}$ are each independently hydrogen, cyano, hydroxy, amino, $H_2NC(O)$-, or a chemical moiety selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyloxy, acyl, (C_1-C_3)alkyl-O-C(O)-, (C_1-C_4)alkyl-NH-C(O)-, $((C_1-C_4)alkyl)_2N$-C(O)-, (C_1-C_6)alkylamino-, di(C_1-C_4)alkylamino-, (C_3-C_6)cycloalkylamino-, acylamino-, aryl(C_1-C_4)alkylamino-, heteroaryl(C_1-C_4)alkylamino-, aryl, heteroaryl, a partially or fully saturated 3- to 6-membered heterocycle, and a partially or fully saturated 3- to 8-membered carbocyclic ring, where the moiety is optionally substituted,

or either R^{4f} or $R^{4f'}$ taken together with R^{4b}, $R^{4b'}$, R^{4c}, or $R^{4c'}$ forms a bond, a methylene bridge or an ethylene bridge; or

(ii) a group having Formula (IC)



(IC)

where R^5 and R^6 are each independently hydrogen or (C_1-C_4)alkyl, and R^7 is (C_1-C_4)alkyl-, halo-substituted (C_1-C_4)alkyl-, (C_1-C_4)alkoxy(C_1-C_4)alkyl-, (C_1-C_4)alkylamino(C_1-C_4)alkyl-, di(C_1-C_4)alkylamino(C_1-C_4)alkyl-, or a partially or fully saturated 4- to 6-membered heterocylic ring containing 1 or 2 heteroatoms independently independently selected from oxygen, sulfur or nitrogen,

or R^5 and R^6 or R^5 and R^7 taken together form a 5- or 6-membered lactone, 4- to 6-membered lactam, or a partially or fully saturated 4- to 6-membered heterocycle containing 1 or 2 heteroatoms independently selected from oxygen, sulfur or nitrogen, where the lactone, the lactam and the heterocycle are optionally substituted;

(iii) an amino group substituted with one or more substituents independently selected from the group consisting of (C_1-C_8)alkyl, aryl$(C_1-$

C_4)alkyl, a partially or fully saturated (C_3-C_8)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_3)alkoxy(C_1-C_6)alkyl, heteroaryl(C_1-C_3)alkyl, and a fully or partially saturated heterocycle; or

(iv) an (C_1-C_6)alkyl group substituted with one or more substituents independently selected from the group consisting of hydroxy, (C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino (C_1-C_3)alkylsulfonyl, (C_1-C_3)alkylsulfamyl, di((C_1-C_3)alkyl)sulfamyl, acyloxy, a fully or partially saturated heterocycle, and a fully or partially saturated cycloalkyl;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit activity disorder (ADHD), Parkinson's disease, and type II diabetes. In a preferred embodiment, the

method is used in the treatment of obesity, ADHD, alcoholism, and/or tobacco abuse.

Compounds of the present invention may be administered in combination with other pharmaceutical agents. Preferred pharmaceutical agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin™ and Concerta™), atomoxetine (e.g., Strattera™), and amphetamines (e.g., Adderall™)) and anti-obesity agents, such as apo-B/MTP inhibitors, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin concentrating hormone receptor antagonists, leptin, leptin analogs, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists, thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and the like.

The combination therapy may be administered as (a) a single pharmaceutical composition which comprises a compound of the present invention, at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two separate pharmaceutical compositions comprising (i) a first composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier. The

pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

Yet another aspect of the present invention includes a pharmaceutical kit for use by a consumer to treat diseases, conditions or disorders modulated by cannabinoid receptor antagonists in an animal. The kit comprises a) a suitable dosage form comprising a compound of the present invention; and b) instructions describing a method of using the dosage form to treat diseases, conditions or disorders that are modulated by cannabinoid receptor (in particular, the CB1 receptor) antagonists.

Another embodiment includes a pharmaceutical kit comprising: a) a first dosage form comprising (i) a compound of the present invention and (ii) a pharmaceutically acceptable carrier, excipient or diluent; b) a second dosage form comprising (i) an additional pharmaceutical agent described herein, and (ii) a pharmaceutically acceptable carrier, excipient or diluent; and c) a container.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched. For example, the term "(C_1-C_6)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy, acyl (e.g., alkanoyl), alkylamino, dialkylamino, and alkylthio group have the same definition as above. When indicated as being "optionally substituted", the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls) independently selected from the group of substituents listed below in the definition for "substituted." "Halo-substituted alkyl" refers to an alkyl group substituted with one or more halogen atoms (e.g., fluoromethyl,

difluoromethyl, trifluoromethyl, perfluoroethyl, and the like). When substituted, the alkane radicals or alkyl moieties are preferably substituted with 1 to 3 fluoro substituents, or 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_4)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), hydroxy(C_2-C_3)alkylamino, or keto (oxy), and more preferably, 1 to 3 fluoro groups, or 1 substituent selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_6)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, (C_1-C_3)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino.

The terms "partially or fully saturated carbocyclic ring" (also referred to as "partially or fully saturated cycloalkyl") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the carbocyclic ring is generally a 3- to 8-membered ring (preferably, 3- to 6-membered ring). For example, partially or fully saturated carbocyclic rings (or cycloalkyl) include groups such as cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclpentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, norbornyl (bicyclo[2.2.1]heptyl), norbornenyl, bicyclo[2.2.2]octyl, and the like. When designated as being "optionally substituted", the partially saturated or fully saturated cycloalkyl group may be unsubstituted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted carbocyclic ring also includes groups wherein the carbocyclic ring is fused to a phenyl ring (e.g., indanyl). The carbocyclic group may be attached to the chemical entity or moiety by any one of the carbon atoms within the carbocyclic ring system. When substituted, the carbocyclic group is preferably substituted with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_6)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-

C_4)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), hydroxy(C_2-C_3)alkylamino, or keto (oxy), and more preferably 1 or 2 from substituents independently selected from (C_1-C_2)alkyl, 3- to 6-membered heterocycle, fluoro, (C_1-C_3)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino. Similarly, any cycloalkyl portion of a group (e.g., cycloalkylalkyl, cycloalkylamino, etc.) has the same definition as above.

The term "partially saturated or fully saturated heterocyclic ring" (also referred to as "partially saturated or fully saturated heterocycle") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 6-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently independently selected from sulfur, oxygen or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, N-methylpyrrolidinyl, imidazolidinyl, imidazolinyl, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, and the like. When indicated as being "optionally substituted", the partially saturated or fully saturated heterocycle group may be unsubstiuted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted heterocyclic ring includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, etc.). When substituted, the heterocycle group is preferably substituted with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_2-C_4)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), or keto (oxy), and more preferably with 1 or 2

substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_6)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, or fluoro. The heterocyclic group may be attached to the chemical entity or moiety by any one of the ring atoms within the heterocyclic ring system. Similarly, any heterocycle portion of a group (e.g., heterocycle-substituted alkyl, heterocycle carbonyl, etc.) has the same definition as above.

The term "aryl" or "aromatic carbocyclic ring" refers to aromatic moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 10-membered aromatic carbocyclic ring(s). When indicated as being "optionally substituted", the aryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.). When substituted, the aromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, or (C_1-C_4)alkoxy. The aryl group may be attached to the chemical entity or moiety by any one of the carbon atoms within the aromatic ring system. Similarly, the aryl portion (i.e., aromatic moiety) of an aroyl or aroyloxy (i.e., (aryl)-C(O)-O-) has the same definition as above.

The term "heteroaryl" or "heteroaromatic ring" refers to aromatic moieties containing at least one heteratom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl,

thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, etc.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. When indicated as being "optionally substituted", the heteroaryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." When substituted, the heteroaromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, (C_1-C_4)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino. The heteroaryl group may be attached to the chemical entity or moiety by any one of the atoms within the aromatic ring system (e.g., imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, or pyrid-6-yl). Similarly, the heteroaryl portion (i.e., heteroaromatic moiety) of a heteroaroyl (i.e., (heteroaryl)-C(O)-O-) has the same definition as above.

The term "acyl" refers to alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C_1-C_6)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, *t*-butylacetyl, etc.), (C_3-C_6)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl,

pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrroyl-2-carbonyl, 1H-pyrroyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions above. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "substituted" specifically envisions and allows for one or more substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Suitable substituents for any of the groups defined above include (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, (C_1-C_6)alkoxy, aryloxy, sulfhydryl (mercapto), (C_1-C_6)alkylthio, arylthio, amino, mono- or di-(C_1-C_6)alkyl amino, quaternary ammonium salts, amino(C_1-C_6)alkoxy, aminocarboxylate (i.e., (C_1-C_6)alkyl-O-C(O)-NH-), hydroxy(C_2-C_6)alkylamino, amino(C_1-C_6)alkylthio, cyanoamino, nitro, (C_1-C_6)carbamyl, keto (oxy), acyl, (C_1-C_6)alkyl-CO_2-, glycolyl, glycyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thio(C_1-C_6)alkyl-C(O)-, thio(C_1-C_6)alkyl-CO_2-, and combinations thereof. In the case of substituted combinations, such as "substituted aryl(C_1-C_6)alkyl", either the aryl or the alkyl group may be substituted, or both the aryl and the alkyl groups may be substituted with one or more substituents (typically, one to three substituents

except in the case of perhalo substitutions). An aryl or heteroaryl substituted carbocyclic or heterocyclic group may be a fused ring (e.g., indanyl, dihydrobenzofuranyl, dihydroindolyl, etc.).

The term "halo" refers to a chloro, bromo, fluoro or iodo group.

The term "solvate" refers to a molecular complex of a compound represented by Formula (I) or (II) (including prodrugs and pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups

and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "animal" refers to humans (male or female), companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry.

The terms "treating", "treat", or "treatment" embrace both preventative, i.e., prophylactic, and palliative treatment.

The terms "modulated by a cannabinoid receptor" or "modulation of a cannabinoid receptor" refers to the activation or deactivation of a cannabinoid receptor. For example, a ligand may act as an agonist, partial agonist, inverse agonist, antagonist, or partial antagonist.

The term "antagonist" includes both full antagonists and partial antagonists, as well as inverse agonists.

The term "CB-1 receptor" refers to the G-protein coupled type 1 cannabinoid receptor.

The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of Formula (I) and Formula (II), prodrugs thereof, pharmaceutically acceptable salts of the compounds, and/or prodrugs, and hydrates or solvates of the compounds, salts, and/or prodrugs, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers, and isotopically labeled compounds. Unless specified otherwise, the term "compounds of the present invention" does not include intermediates (1c/d) or (1b).

DETAILED DESCRIPTION

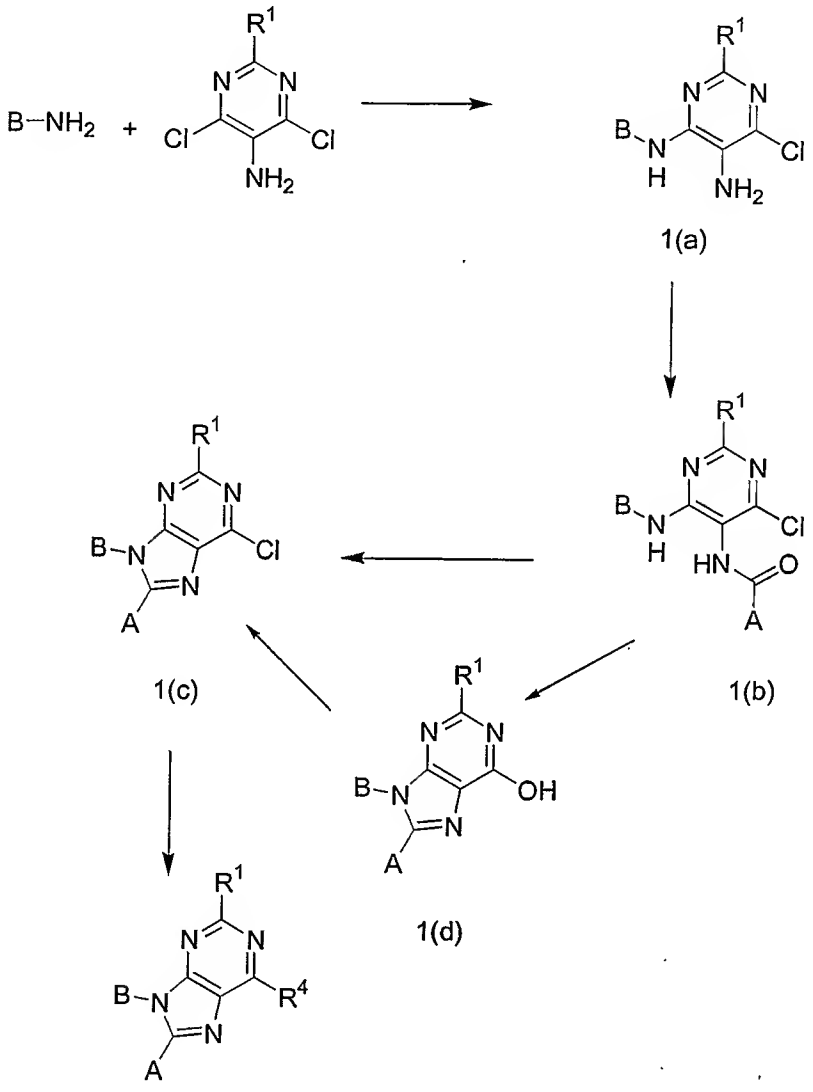
Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing the compounds of the present invention including key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the present invention (including the inventive intermediates). Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of

protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of Formula (I) and (II) can be prepared using the general procedures described by R.J. Chorvat, et al. in J. Med. Chem, **42**, 833-848 (1999) and depicted in Scheme I below.



Scheme I

Intermediate 1(a) may be prepared by reacting the desired amino compound (B-NH_2, where B is as defined above) with 4,6-dichloro-5-aminopyrimidine (available from Sigma-Aldrich, St. Louis, MO) in refluxing aqueous hydrochloric acid (A. Miyashita et al. in Chem. Pharm. Bull., **46**,

390-399 (1998)) or ethoxyethanol at elevated temperatures. Suitable amino compounds (B-NH_2) include those compounds where B is aryl (e.g., aniline) or substituted aryl (e.g., 2-chloroaniline, 2-fluoroaniline, 2,4-dichloroaniline, 2-fluoro-4-chloroaniline, 2-chloro-4-flurooaniline, 2,4-difluoroaniline, and other substituted arylamines). Other commercially available derivatives of 4,6-dichloro-5-aminopyrimidine may be used as a starting material for those compounds of Formula (I) or (II) where R^1 is other than hydrogen (e.g., 2-methyl-4,6-dichloro-5-aminopyrimidine and 2-ethyl-4,6-dichloro-5-aminopyrimidine). For representative literature syntheses of 4,6-dichloro-5-aminopyrimidine derivatives see: A. Albert et al. in J. Chem. Soc., 3832 (1954) and W.E. Hymans in J. Heterocycl. Chem., **13**, 1141 (1976).

Intermediate 1(a) can then be acylated using conventional chemistry well-known to those skilled in the art. For example, intermediate 1(a) may be reacted with the desired aroyl or heteroaroyl chloride in a basic solvent (e.g., pyridine) to produce intermediate 1(b). Alternatively, intermediate 1(a) may be reacted with the desired aroyl or heteroaroyl chloride in a reaction inert solvent (e.g., tetrahydrofuran, methylene chloride, *N,N*-dimethylacetamide). The addition of a suitable base (e.g., triethylamine, diisopropylethylamine) may help facilitate the reaction. Suitable aroyl chlorides include benzoyl chloride, o-chlorobenzoyl chlorides, o-fluorobenzoyl chloride, p-chlorobenzoyl chloride, p-fluorobenzoyl chloride, 2,4-dichlorobenzoyl chloride, 2,4-difluorobenzoyl chloride, and the like.

Intermediate 1(b) may then be cyclized to the 6-chloro-purine intermediate 1(c) by treatment with a condensation agent using analogous procedures and conditions described in U.S. Patent No. 4,728,644, incorporated herein by reference. In a preferred method, intermediate 1(b) can be refluxed in a weak acid (e.g., acetic acid) or sulfuric acid in an appropriate solvent (e.g., isopropyl alcohol, toluene) to provide the hydroxy purine intermediate 1(d) followed by refluxing in phosphorous oxychloride, toluene in the presence of phosphorous oxychloride and triethylamine, or 2,6-lutidine in phosphorous oxychloride to give intermediate 1(c). In another

preferred method, 1(b) may be directly converted to 1(c) by refluxing in phosphorous oxychloride; an appropriate co-solvent (e.g., toluene) and/or base (e.g., pyridine, triethylamine) may be added to aid in the condensation.

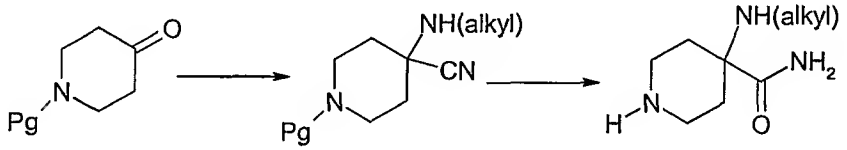
Finally, the R^4 group can be introduced by displacing the chloride on the purine ring at the 6 position.

For compounds of Formula (I) and (II) where R^4 is an amino group, intermediate 1(c) is generally stirred with the desired amine (e.g., substituted or unsubstituted aryl(C_1-C_4)alkylamine, substituted or unsubstituted 2-indanylamine, substituted or unsubstituted cyclohexylamine, substituted or unsubstituted cyclopentylamine, substituted or unsubstituted norboranylamine, hydroxy(C_1-C_6)alkylamine, substituted or unsubstituted heteroarylamine, heteroaryl(C_1-C_3)alkylamine, and substituted or unsubstituted 5- to 6-membered heterocyclic amine (i.e., an amine of Formula (Ia) defined above)). The amine may act as the solvent or a solvent (e.g., ethanol, methylene chloride, etc.) may be added to assist in solubilization of the reactants and/or provide a media having the appropriate refluxing temperature to complete the substitution. The reaction may be heated to accelerate the process. In addition, a suitable base such as triethyl amine may be employed to quench the acid produced in the process. Suitable amino compounds can be either purchased commercially or easily prepared using standard procedures well-known to those skilled in the art.

Compounds of Formula (I) above where R^4 is a primary or secondary amine can be alkylated, sulfonated and/or acylated to provide additional derivatives (e.g., alkylamines, dialkylamines, sulfonamides, amides, carbamates, ureas, etc.) using standard procedures well-known to those skilled in the art.

Compounds of Formula (I) above where R^4 is an amino acid may be prepared as described by A.M. Shalaby et al. in J. Chem. Res., 134-135 (1998). These materials may be further elaborated to amides and esters using standard procedures well-known to those skilled in the art.

Numerous amine compounds of Formula (IA) are available from commercial sources or prepared by known methods readily available to those skilled in the art. Representative preparations of amine compounds of Formula (IA) are illustrated in the Examples below. The preparation of 4-aminopiperidine-4-carboxamide groups of Formula (IA) and 4-amino-4-cyano piperidine groups of Formula (IA) and their benzyl protected precursors are described by P.A.J. Janssen in US Patent No. 3,161,644, C. van de Westeringh et al. in J. Med. Chem., **7**, 619-623 (1964), and K.A. Metwally et al. in J. Med. Chem., **41**, 5084-5093 (1998) where the above 4-amino groups are unsubstituted, monosubstituted, disubstituted, or part of a heterocyclic ring. Related bicyclic derivatives are described by K. Frohlich et al. in Tetrahedron, **54**, 13115-13128 (1998) and references contained therein. Spiro-substituted piperidines of formula (IA) are described by P.A.J. Janssen in US Patent No. 3,155,670, K. A. Metwally et al. in J. Med Chem., **41**, 5084-5093 (1998), T. Toda et al. in Bull. Chem. Soc. Japan, **44**, 3445-3450 (1971), and W. Brandau and S. Samnick in WO 9522544. The preparation of 3-aminoazetidine-3-carboxamide is described by A.P. Kozikowski and A.H. Fauq in Synlett, 783-784 (1991). The preparation of preferred 4-alkylaminopiperidine-4-carboxamide groups of Formula (IA) are depicted in Scheme II below.



2(a) 2(b) 2(c)

Scheme II

The amino group of 4-piperidinone is first protected to provide intermediate 2(a). A useful protection group is benzyl. 4-piperidinone and derivatives thereof may be purchased commercially from a variety of sources (e.g., Interchem Corporation, Paramus, NJ and Sigma-Aldrich Co., St. Louis, MO). Piperidinone 2(a) is then reacted with the desired alkylamine and potassium cyanide in an aqueous HCl/ethanol solvent mixture at about 0-30

°C. The cyano group is converted to the corresponding amide with acid and water. The protecting group is then removed using conventional methods for the particular protecting group employed. For example, a benzyl protecting group may be removed by hydrogenation in the presence of Pd/C.

For compounds of Formula (I) and (II) where R^4 is an aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl group, the chlorine in intermediate 1(c) may first be displaced with a cyano group (e.g., treating with tetrabutylammonium cyanide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in an aprotic solvent (e.g., acetonitrile) at room temperature). See, e.g., Hocek, et al. Collect. Czech. Chem. Commun. 60,1386 (1995). The cyano can then reduced to the alkyl amine using standard reduction methods well-known to those skilled in the art (e.g., treating with DIBAL or hydrogen in the presence of Pd/C). The amino group can then be alkylated using standard reductive alkylation procedures. Generally, a Schiff base is formed by reacting the amine with the desired ketone or aldehyde in a polar solvent at a temperature from about 10 °C to about 140 °C for about 2 to about 24 hours in the presence of 3 Å molecular sieves. Typically, an equivalent or a slight excess of the amino compound is added to the ketone or aldehyde. Suitable polar solvents include methylene chloride, 1,2-dichloroethane, dimethylsulfoxide, dimethylformamide, alcohols (e.g., methanol or ethanol), or mixtures thereof. A preferred solvent is methanol. In the same reaction vessel, the imine may then be reduced to the secondary amine in the presence of a reducing agent at a temperature from about 0 °C to about 10 °C and then warmed to a temperature from about 20 °C to about 40 °C for about 30 minutes to about 2 hours. Suitable reducing agents include pyridine•borane complex and metal borohydrides, such as sodium borohydride, sodium triacetoxy borohydride and sodium cyanoborohydride. Suitable aldehydes or ketones include paraformaldehyde, acetaldehyde, acetone, benzaldehyde, and the like.

Alternatively, the amino alkyl group may be introduced using the methods described by Hocek, et al. in Tetrahedron, 53(6), 2291-2302

(1997). The 6-chloropurine intermediate 1(c) is converted to the 6-acetylpurine compound by reacting intermediate 1(c) with 1-ethoxyvinyl)tri-*n*-butyltin under $Pd(PPh_3)_4$ catalysis followed by hydrolysis using a mixture of acetone and aqueous HCl (or DMF/aq. HCl mixture) at reflux temperatures to give the acetylated purine. The acetyl group is then easily converted to an amine or substituted amine by reductive amination, a process well-known to those skilled in the art. An examplary procedure employs the desired amine salt (e.g., ammonium chloride, methylammonium chloride, allylammonium chloride, cyclopropylammonium chloride, cyclohexylammonium chloride, dimethylammonium chloride, benzylammonium chloride, etc.) and a reducing agent (e.g., $NaBH_4$, $NaBH_3CN$, or triacetoxyborohydride) in polar solvent at room temperature. See Abdel-Magid, et al., J. Org. Chem., **61**, 3849-3862 (1996) for a wide variety of aldehydes, ketones and amines that may be used in either the reductive alkylation of the 6-aminopurine or the reductive amination of the 6-acetylpurine.

For those compounds of Formula (I) and (II) where R^4 is an unsubstituted or substituted alkoxy group, intermediate I(c) may be treated with the desired alcohol in the presence of a base (e.g., potassium t-butoxide) and an aprotic solvent (e.g., THF). Suitable alcohols can be either purchased commercially or easily prepared using standard procedures well-known to those skilled in the art.

Alternatively, compounds of Formula (I) or (II) where R^4 is a hydroxy or alkoxy substituted alkyl group may be produced by replacing the chlorine group of intermediate 1(c) with the desired electrophile using procedures described by Sugimoto, et al., in Tetrahedron Letters, **40**, 2139-2140 (1999). The 6-chloropurine intermediate 1(c) is reacted with lithium *n*-butane-tellurolate (tellurium reacted with n-butyllithium) in an aprotic solvent (e.g., THF) at -78°C followed by the addition of the desired electrophile (e.g., acetaldehyde, benzaldehyde, acetone, methylethyl ketone, etc.) and then warmed to room temperature to form the desired hydroxyalkyl derivative. Alternately, the hydroxy derivative may be formed using the procedures

described by Leonard, et al, in J. Org. Chem., **44**(25), 4612-4616 (1979). The 6-chloropurine intermediate 1(c) is treated with n-butyl lithium to form the carbanion at -78°C followed by reaction with the desired electrophile (e.g., ketone or aldehyde) to form the hydroxyalkyl derivative.

In yet another approach, a 6-aroylpurine compound can be prepared by the procedures described by Miyashita, et al, in Chem. Pharm. Bull, **46**(30), 390-399 (1998). The aroyl group can then be reduced to the corresponding secondary alcohol by treating with a reducing agent such as lithium alumunium hydride. The tertiary alcohol can be obtained upon treatment with an alky metal reagent, such as an alkyl Grignard reagent, in a suitable solvent (e.g., tetrahydrofuran, diethyl ether). Finally, an amine could be introduced by reductive amination (see above).

In the above examples, the resultant hydroxyalkyl group can then be alkylated or acylated to form the desired alkoxy or acylate (e.g., (alkyl)-C(O)-O-, (aryl)-C(O)-O-, (heteroaryl)-C(O)-O-, etc.) using standard procedures well-known to those skilled in the art. Alternatively, the hydroxy group may be condensed with other moieties to provide a variety of substituents (e.g., sulfamyl, sulfonyl, etc.). The aminoalkyl group could be modified in a similar fashion to give amides, sulfonamides, etc.

The R^4 group may be attached to the pyrimidine moiety either after (as described above) or prior to cyclization to the purine. Scheme III below illustrates the introduction of the R^4 group prior to cyclization to the purine.